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Considerations on Biologicals for Patients with allergic disease in times of the COVID-19 pandemic: an EAACI Statement

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Abstract

The outbreak of the SARS-CoV-2-induced Coronavirus Disease 2019 (COVID-19) pandemic re-shaped doctor-patient interaction and challenged capacities of healthcare systems. It created many issues around the optimal and safest way to treat complex patients with severe allergic disease. A significant numberof the patients are on treatment with biologicals and clinicians face the challenge to provide optimal care during the pandemic. Uncertainty of the potential risks for these patients is related to the fact that the exact sequence of immunological events during SARS-CoV-2 is not known. Severe COVID-19 patients may experience a "cytokine storm" and associated organ damage characterized by an exaggerated release of proinflammatory type 1 and type 3 cytokines. These inflammatory responses are potentially counteracted by anti-inflammatory cytokines and type 2 responses. This expert based EAACI statement aims to provide guidance on the application of biologicals targeting type 2 inflammation in patients with allergic disease.

Currently, there is very little evidence for an enhanced risk of patients with allergic diseases to develop severe COVID-19 with studies focusing on severe allergic phenotypes lacking. At present, non-infected patients on biologicals for the treatment of asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps or chronic spontaneous urticaria should continue their biologicals targeting type 2 inflammation via self-application. In case of an active SARS-CoV-2 infection, biological treatment needs to be stopped until clinical recovery and SARS-CoV-2 negativity is established and treatment with biologicals should be re-initiated. Maintenance of add-on therapy and a constant assessment of disease control, apart from acute management is demanded.

Capsule summary

1. Current evidence does not suggest a higher risk for severe COVID-19 disease in allergic individuals but data specifically investigating severe allergic phenotypes is missing.
2. Severe COVID-19 patients may experience a "cytokine storm" and associated organ damage, particularly acute respiratory distress syndrome, acute kidney and liver failure, myocarditis and disseminated vascular coagulation. These manifestations are characterized by an exaggerated release of proinflammatory type 1 and 3 cytokines. These type 1 and type 3-driven inflammatory responses are potentially counteracted by anti-inflammatory cytokines, such as IL-10 and TGF-β, as well as potentially type 2 responses.
3. The key recommendation for an accurate management of non-infected patients on biologicals targeting type 2 inflammation because of an underlying severe allergic disease is the continuation of their drug regimen with close follow-up.
4. All patients with a COVID-19 disease should pause the application of biologicals until viral clearance. As per WHO recommendations mild disease can be treated at home with close monitoring, while moderate and severe cases should be hospitalized.

Introduction

The outbreak leading to the pandemic of SARS-CoV-2-induced Coronavirus Disease 2019 (COVID-19) has pushed health care systemsto the limits of their capacity across the globe. This infection can cause severe respiratory illness and multi-organ failure with clinical presentations greatly resembling SARS-CoV-1 and MERS-CoV, resulting in intensive care unit (ICU) admission and high mortality. We discuss immunological and clinical considerations for patients on biologic agents (biologicals)targeting the type 2 inflammatory response due to difficult-to-treat allergic diseases in the context of COVID-19.

Immunological features of SARS-CoV-2 infection in the context of type 2 inflammation

Both innate and adaptive immune responses participate in anti-viral immunity. The interactions between SARS-CoV-2 and both arms of the immune system have been poorly clarified until now, particularly in the view of asymptomatic individuals, patients with mild disease, and those who fully recover. Natural killer cells are involved in control of the acute phase of the viral infection, whereas CD8+ T cells are the key player in the following steps.[1]Antibody-secreting cells and T follicular helper cells are instrumental in the production of specific anti-viral IgA, IgM and IgG antibodies early on.[2-4]Antibody-dependent macrophage activation as well as lymphocyte and macrophage pyroptosis (an excessive form of inflammatory cell apoptosis) might occur and contribute to more severe tissue damage, as described in SARS-CoV infection.[5-8]Among mediators, type I interferons (type I IFN) play a central role. In other coronavirus infections such as severe acute respiratory syndrome (SARS), type I IFN are critical for the initiation of immune response and virus clearance. Delayed production of type I IFN and aninsufficient cytotoxic responseis associated with a more severe clinical disease. Observations from SARS or Middle East respiratory syndrome (MERS)[5,8] and, more recently, COVID-19 patients[9]suggest an overshooting immune response in severe cases with wide-spread lung damage and disease aggravation around 7-14 days after onset. Those severe COVID-19 patients may also experiencea picture of a so-called “cytokine storm” and associated organ damage, particularly acute respiratory distress syndrome, acute kidney and liver failure, myocarditis and disseminated vascular coagulation. These manifestations are characterized byan exaggerated release of proinflammatory

cytokines, such as IL-1β, IL-6, IL-8, TNF-α and many more (Figure 1).Consequently, these highly increased proinflammatory cytokines are believed to be potential targets for biological therapy.These type 1 and type 3-driven inflammatory responses are counteracted by anti-inflammatory cytokines,such as IL-10 and TGF-β, as well as potentially type 2 responses. Moreover, eosinophils have been reported to play a role in virus response.[10]Lower eosinophil counts were reported in association with severe cases, while an elevated eosinophil count was associated with a better prognosis[9] although no functional relationship has been established so far and this finding may be an epiphenomenon. Thus, probably all shades of cytokine responses (type 1 and type 3, type 2, and regulatory cytokines) are required in the healing of SARS-CoV-2 infection. An appropriate induction and downregulation of individual response batteries is necessary to achieve an efficient viral clearance, an avoidance of excessive inflammatory reaction and irreversible tissue damage (Figure 2).

SARS-CoV-2 infection and allergic disease

In line with a paucity of mechanistic data on COVID-19 in the context of type 2 inflammation, knowledge on the disease course in patients treated with biologicals targeting type 2 inflammation due to severe asthma or other atopic diseases, such as CSU, AD and CRSwNP, is scarce to absent. To our knowledge by April 12th 2020, only 6 studies presented disease characteristics of SARS-CoV-2 infection on patients with allergy or atopic diseases as a co-morbidity (Table 1). While, in a study including 1591 patients infected with SARS-CoV-2 and admitted to ICUs of Lombardy, Italy, asthma was not referred to as a specific comorbidity and grouped under "others".[11] Allergic disease seemed to have no influence on presented symptoms and the course of the disease.[12-15] None of these patients were on biologicals to treat their pre-existing allergic disease. In a recent report from the COVID-19-Associated Hospitalization Surveillance Network based on data from 14 US states from March 1st-30th 2020 17% of hospitalized COVID19 patients had asthma as a co-morbidity. The highest percentage was in the 18-49 years old patient group with 27.3% asthmatics. No information on severity of the disease and therapy has been provided. This supports the importance of a prospective assessment of atopic diseases in the context of COVID19.

Biological therapies targeting type 2 inflammation: key issues

In the past years, new biological therapies for severe asthma, atopic dermatitis (AD), chronicrhinosinusitis with nasal polyps (CRSwNP) and chronic spontaneous urticaria (CSU) have been developed targeting different aspects of the type 2 immune response.[16-24] Anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) are approved for severe asthma with peripheral eosinophilia, uncontrolled under high intensity treatment. Benralizumab, a monoclonal antibody that binds to the α subunit of IL-5 receptor (IL-5Rα)[25] was also recently approved for uncontrolled eosinophilic severe asthma. Dupilumab, a monoclonal antibody directed against the α subunit of the IL-4 receptor (IL-4Rα) acting as a dual antagonist of both IL-4 and IL-13 was approved for uncontrolled severe type 2 asthma, moderate to severe AD and CRSwNP. Omalizumab, a humanized monoclonal anti-IgE antibody, has also been approved for IgE-mediated persistent allergic asthma and CSU.

The spread of the disease prompted allergists and immunologists to reduce their service to the acceptable minimum and important guidance of patients receiving biological therapies is limited, so insecurity on how to manage their disease in case of an infection may occur. To date the role of type 2 cytokines in the pathogenesis and severity of COVID-19 is not well established and therefore guidance of patients on biologicals targeting pathways of the allergic response during this pandemic is scarce. Main questions in this context area.) to what extent is there an increased risk of allergic patients on biologicals targeting type 2 inflammation to being infected or developing severe disease upon SARS-CoV-2 infection b.) the degreeof side effects that arise from potential immunosuppressive biologicals against the benefits of controlling the diseasessuch as severe asthma, AD, CRSwNP or CSU.

Blocking type 2 inflammation and viral infections

The low number of reports of patients on biologicals targeting type 2 disease is encouraging since type 2 diseases may predispose patients to viral infections due to compromised barriers.[26-30]Consequently, epidemiologic evidence closely links virus infections to both development and exacerbation of allergic diseases.[31-33] The infection and persistence of respiratory viruses is attributed to impaired innate immune responses and a predisposition to mount strong type 2 immune responses. In line with this argumentation some of these drugs provided evidence for a

reduction of viral infections in asthmatics such as anti-IgE treatment with omalizumab. Itmay cause anti-inflammatory and immunomodulatory effects by restoring the capacity of human plasmacytoid dendritic cells (pDCs) to produce IFN-α, increasing antiviral activity and reducing viral-induced asthma exacerbations [31,34].In severe asthma, clinical trials showed that rates of respiratory infections (upper respiratory tract infection, viral upper respiratory tract infection, influenza) were lower or similar in the anti-IL-5 monoclonal antibody (mAb)-and dupilumab-treated groups compared to placebo (Table 2). No data are available on the impact of anti-IL-5 mAb and dupilumabon virus-induced exacerbations and antiviral responses.For dupilumab, anincreased risk of herpes-virus reactivation has been reported in real-life uncontrolled studies and case reports. The pathogenesis of cytokine storm-related tissue injury has been repeatedly reported in COVID-19, dominated by proinflammatory type 1 and type 3 associated cytokines and linked inflammasome activationand neutrophilia. It has been reported that type 2 response and Treg response can antagonize these effects and may be beneficial.[35]In this context, the inhibition of type 2 response in severe and critical COVID-19 cases may cause an aggravation of the disease. Therefore, such biologicals should be discontinued in very severe disease. Due to their long in vivo half-life in the range of a few weeks, it remains unclear to which extent such an action would impact the acute management and what the risk of losing disease control and co-morbidity later on could be. Recent systematic reviews on approved biologicals in severe asthma showed that biologicals targeting IL-5-signalling pathway (mepolizumab, reslizumab and benralizumab) slightly increase drug-related adverse events (AE) in severe eosinophilic asthma.[36] For anti-IgE (omalizumab) and anti-IL-4Rα (dupilumab) treatments rate ratios were rather small.[36]Benralizumab and omalizumab showed an increase in AEs with low to moderate certainty in severe allergic asthma.[37]There was an increased rate of dupilumab-related AEs (low certainty) in severe asthma.[38]Data from clinical trials demonstrated good safety profiles of biologicals with regards to viral infections of the upper respiratory tract (Table 2).[36-38]

Practical and clinical recommendations

Recommendations from national societies

Time restrictions did not allow for official guidelines to be published so far. However, several societies issued statements on the use of biologicals during the COVID-19 pandemic (Table 3). A consensus-based ad-hoc expert panel of allergy/immunology specialists from the US and Canada

recommends continuing administration of biologicals in patients with proven efficacy and converting the patient to a prefilled syringe for potential home administration if this is available or otherwise in-office application can occur with a plan to transition to home administration.[39] Initiation of biologic therapy for AD should be weighed very carefully, but it remains a viable option as this is administered at home. In a recent communication, the European Task Force on Atopic Dermatitis (ETFAD) suggested that targeted treatment selectively interfering with type 2 inflammation, such as dupilumab, is not considered to increase the risk for viral infections and might thus be preferred compared to immunosuppressive treatments such as cyclosporine in a situation such as the COVID-19 pandemic, although stressing that this theoretical advantage is not supported by robust clinical data.[40] The British Society of Allergy and Clinical immunology suggests to defer commencement of omalizumab in new patients with chronic urticaria until COVID-19 restrictions are lifted and transitioning to home therapy after the second dose if not contraindicated (https://www.bsaci.org/announcements/modifications-for-adult-allergy-services-during-covid-19-pandemic).None of these statements recommended discontinuation so far.

EAACI statement on the management of allergic disease with type 2 targeting biologicals during COVID-pandemic

The key recommendation for an accurate management of non-infected patients on biologicals targeting type 2 inflammation because of an underlying severe allergic disease is the continuation of their drug regimen with close follow-up. During the COVID-19 pandemic, social distancing is encouraged for everybody and home application of the biologicals should be practiced if doable since an exacerbation of their disease requiring hospitalization would expose them to an increased risk of acquiring a SARS-CoV-2 infection. If that is not possible it should be ensuredthat the application takes place in a safe environment (Figure 3).

All patients with a SARS-CoV-2 infection, irrespective of the severity of the infection should withhold the application of biologicals until recovered.

If patientsdisplay mild clinical manifestations that allow home isolation, telemedical follow-up by the physician in charge should take place to ensure proper management, and background controller treatment (topical steroids or other controller medications as recommended by current guidelines) should be continued, as describedfor asthma, AD, CRSwNP and CSU[22,23,41-45].Surgical interventions for CRSwNP should be delayed in any case possible.

In case of hospital admission for moderate, severe or critical SARS-CoV-2 infection,management of the allergic disease should be in accordance with current guidelinesby involving the respective subspecialties. In particular for asthma inhalation therapy use preferably metered dose inhalations with chambers that are not to be shared and pulmonary function tests should be performed only if highly necessary(Figure 3).

Once resolution/recovery of the disease is established (e.g. via a negative SARS-CoV-2 test)but no shorter than 2 weeks post onset of the disease/positive testing, the re-administration of the biological should be re-initiated (Figure 3).

Conclusions

In conclusion, current evidence does not suggest a higher risk for severe COVID-19 in allergic individuals but data that allows estimating the risk of severe allergic phenotypes in case of SARS-CoV-2 infection is missing. Treatment of patients on biologicals targeting type 2 inflammation in allergic disease should be maintained in non-infectedindividuals. In case of an infection withholding the treatment is recommended until recovery. Additional data on those patients with more severe phenotypes will provide more insight to define more precisely the risk profile of individuals with allergic disease who are of elevated risk.The collection of such data is imperative for future data-informed adaptations of these guidelines.

Figure Legends

Figure 1: Cellular networks during SARS-CoV-2 Infection

Initially, infection with the SARS-CoV-2 induces both humoral and cellular (innate and adaptive) immune responses. Recruitment of antibody-secreting cells (ASC) and interaction with T follicular helper cells (Tfh) occurs early before the resolution of symptoms and leads to the production of IgA, IgM andIgG against viral nucleoprotein (NP) and surface spike protein receptor binding domain (RBD). SARS-CoV-2 binding antibodies may participate in tissue damage by macrophage activation via FcγRI.

SARS-CoV-2 infects several types of cells (alveolar lung cells, macrophages, endothelial cells, lymphocytes) stimulating type I IFN production which is crucial for the protection of uninfected cells and the enhancement of natural killer (NK) cell cytotoxic activity.

Virus-cell interactions lead to the release of mediators. The secretion of large amounts of cytokines and chemokines is promoted in infected cells and effector cell populations in response to virus. These mediators in turn, alert tissue-resident lymphocytes (including also innate lymphoid cells, ILCs) and recruit other leukocytes, predominantly in the lungs.

Dendritic cells function as sensor cells and present virus antigens to T cells. This process leads to T cell activation and differentiation, including the production of cytokines associated with Th1 and Th17 profile and subsequently activates CD8+ cytotoxic T cells. Both, inflammation and cell damage, induce and result in the release of danger signalsand alarmins (IL-33, IL-25, TSLP) that may promote both Th2 cells and ILC2 cells.The immune network during the course of infection includes the involvement of regulatory T (Treg) cells, able to secrete IL-10 and TGF-β.

Figure 2. Thehypothesis of a favorable evolution of SARS-CoV-2 infection in the context of type2 cytokine and regulatory cytokine responses.

The hypothetical evolution of the anti-viral immune response during SARS-CoV-2 infection may unfold as following: Lung injury triggered by virus is propagated by innate and adaptive immune system. Adaptive responses are triggered shortly after activation of the innate system. During the infection course, a dynamic balance between pro-inflammatory type 1 and Th17 cells as well as Treg populations and anti-inflammatory type 2 responses are upregulated. Both, high levels of certain type 2 (IL-4, IL-13) and regulatory cytokines (IL-10, TGF-β) could protect from worsening of lung tissue damage.

Figure 3: Clinical Algorithm on the use of biologicals for the treatment of allergic diseases in the context of COVID-19

Non-infectedpatients on biologicals for the treatment of asthma, AD, CRSwNP or CSU should continue their biologicalstargeting type 2 inflammation via self-application. In case of an active SARS-CoV-2 infection and moderate-to-severe COVID-19,biological treatment needs to be stopped until clinical recovery and SARS-CoV-2 negativity is established. Thereafter treatment with biologicals can be re-initiated.

Tables

Table 1. Reports on allergies and atopic diseases in COVID19 patients in scientific literature.

Dong et al. (Wuhan)[13]	Case series of 11 cases of COVID 19 with distinct features 3/11 patients with history of allergic diseases (1 with allergic rhinitis, 1 with atopic dermatitis, 1 with urticaria)
Bhatragu et al. (Seattle)[12]	3/24 patients presented to ICU with severe respiratory failure after previous week of systemic glucocorticoid treatment (outpatient) due to asthma exacerbation while symptomatic for COVID-19
Wang et al. (Wuhan)[14]	2/69 patients with asthma
Zhang et al. (Wuhan)[15]	two and sixteen of 140 patients with chronic urticaria and drug hypersensitivity, respectively, were self-reported
Grasselli G et al. (Lombardy)[11]	Asthma and immunocompromised patients, included anemia, inflammatory bowel disease, chronic respiratory insufficiency, endocrine disorders, chronic pancreatitis, connective tissue diseases, and organ transplant, as well as epilepsy and neurologic disorders were reported under group "other," in a total of 205/1591 patients admitted to ICU
Garg, S. et al. (14 USstates, COVID-NET)[46]	The findings reported in this study have been obtained fromhospitalized COVID-19 patients in USA from March 1st-30th2020. A significant proportion of these patients with available data hadasthma as co-morbidity: 18-49y (n=12/44; 27.3%; 50-64y (n=7/53; 13.2%) ≥ 65y (8/62; 12.9%).
Dreher M et al. (Aachen, Germany)[47]	Patients with respiratory disease are more likely to develop ARDS (58 vs 42%, 14 vs. 11 patients, n=50) with asthma 4 vs. 2 patients.

Table 2. Viral infections as an adverse event during biological treatment in phase 3, meta-analysis and long-term follow-up studies.

Biological	Target structure	Application interval	Infection rate (%)Biological/placebo (Total n/group)	Reference	Indication
Benralizumab	IL-5R alpha	Q4W	n = 1926 n = 25 Viral URTI[X] 24.1/0 (14/11)	Busse WW et al. Lancet Respir Med. 2019;7:46-59.[1] Busse WW et al. AAAAI Annual Meeting; March 13-16, 2020; Philadelphia, PA.[48]	Severe uncontrolled eosinophilic asthma
		Q8W	n = 61 Viral upper respiratory tract infections 12.5/13.8 (32/29)	Busse WW et al. Lancet Respir Med. 2019;7:46-59.[1] Busse WW et al. AAAAI Annual Meeting; March 13-16, 2020; Philadelphia, PA.[48]	Severe uncontrolled eosinophilic asthma
Dupilumab	IL-4R alpha	various (QW, Q2W, Q4W, Q8W), placebo	n=422, URTI (5.7-8.3/7.3), Influenza (0-5.7/1.2), HSV1 (1.8-6.0/3.7), Viral infections (0-1.2/3.7)	Worm et al., JAMA Dermatol. 2016;156(2):131-143.[2]	Atopic dermatitis
		combined (200mg / 300mg Q2W),	n=1897, viral upper respiratory tract infections (18.2/19.6), upper respiratory tract infections (11.6/13.6),	Castro et al., NEJM. 2018;378:2486-2496.[3]	Moderate to severe uncontrolled Asthma

		placebo	influenza (5.9/8.0)		
		300mg Q2W, placebo	n=210, Viral URTI (9/18), Influenza (3/6)	Rabe et al., NEJM. 2018;378:2475-2485.[4]	Severe steroid dependent Asthma
		Adolescence. 200/300mg Q2W, 300mg Q4W, placebo	n=250, URTI (7.2-12.2/17.6), HSV infections (1.2-4.8/3.5)	Simpson et al., JAMA Dermatol. 2019;156(1):44-56.[5]	Atopic dermatitis
		300mg Q2W, placebo	n=276 URTI (5.4-6.7/12.7)	Bachert et al., Lancet. 2019;394:1638-1650.[6]	Chronic Rhino-Sinusitis with nasal polyps
		300mg QW/Q2W, placebo	n=1379 URTI (3-5/2), HSV (0-3/1), HSV1 (2-4/2), HSV2 (1/1) VZV (herpeszoster) (0-1/1),	Simpson et al., NEJM. 2016;375(24):2335-2348.[7]	Atopic dermatitis
		300mg QW/Q2W, placebo	n=740 URTI (10-14/10) Influenza (3-4/5) HSV (2-3/1), VZV (herpeszoster) (<1-1/2), HSV1 (4-5/3)	Blauvelt et al., Lancet. 2017;389:2287-2303.[8]	Atopic dermatitis

		300mg Q2W, real-life, open label	n=241 URTI (1.2) HSV (<1%)	Faiz et al., JAMA Dermatol. 2019;81(1):143-151.[9]	Atopic dermatitis
		300mg Q2W	n=1491 viral URTI (2.5) Influenza (2.1) HSV1 (4.3)	Deleuran et al., JAMA Dermatol. 2020;82(2):377-388.[10]	Atopic dermatitis
Mepolizumab	Human IL-5	75 mg IV Q4W 100 mg SC Q4W	n = 576 Influenza 5/3 (191/191) 3/3, (194/191) Viral URTI 1/<1 (191/191) 0/<1, (194/191) HSV1 <1/<1 (191/191) <1/<1 (191/191) HSV2 <1/0 (191/191) <1/0 (191/191) Herpes zoster <1/0 (191/191) 1/0 (191/191)	Ortega HG et al., N Engl J Med. 2014;371 (13):1198-1207[11] GlaxoSmithKline. MENSA (MEA115588) - Clinical Study Report, page 643-645, table 7.03. Available from: https://www.gsk-studyregister.com/en/trial-details/?id=115588. Accessed April 7, 2020.	Severe, eosinophilic asthma
		100 mg SC/ Q4W	n = 135 Influenza 4/2, (69/66) Viral URTI 1/2 (69/66) Herpes zoster 0/2 (69/66)	Bel EH et al., N Engl J Med. 2014;371(13):1189-1197.[12] GlaxoSmithKline. SIRIUS (MEA115575) Clinical Study Report, page 450-51, table 7.04. Available from:	Severe, eosinophilic, steroid dependent asthma

				https://www.gsk-studyregister.com/en/trial-details/?id=115575. Accessed April 7, 2020.	
		100 mg/ Q4W	n = 551 Influenza 3/1, (273/278) HSV1 <1/0, (273/278) Herpes zoster <1/<1, (273/278)	Chupp GL et al., Lancet Respir Med. 2017;5(5):390-400.[13] GlaxoSmithKline. MUSCA (MEA 200862) Clinical Study Report; page 663-664: table 3.02. Available from: https://www.gsk-studyregister.com/en/trial-details/?id=200862. Accessed April 7, 2020.	Severe, eosinophilic asthma
Omalizumab	IgE	Q2W or Q4W	Any rhinovirus infection 3.3/3.4 (243/84)	Esquivel A et al., Am J Respir Crit Care Med. 2017;196(8):985-992.[14]	Severe allergic asthma
Reslizumab	Human IL-5	3.0 mg/kg (iv) /Every 4 weeks	URTI 9/9 (1028/730)Influenza 3/5 (1028/730)	Virchow JC et al., J Allergy Clin Immunol Pract. 2020;8(2):540–548.e1.[15]	Severe, eosinophilic asthma

[x]: **Any rhinovirus infection,** CRSwNP Chronic Rhinosinusitis with Nasal Polyps

Table 3. Recommendations of national societies and international societies on the management of patients with severe allergic disease

ETFAD[40]	To continue all immune-modulating treatments, including immuno-suppressive therapy, since exacerbations of underlying diseases can have a large negative impact on patients' immunity. "Targeted treatment selectively interfering with type 2 inflammation, such as dupilumab, is not considered to increase the risk for viral infections and might thus be preferred compared to conventional systemic immuno-suppressive treatments, such as cyclosporine, in a situation such as the COVID-19 pandemic. However, this theoretical advantage is not supported by robust clinical data."
AAAAI www.aaaai.org based on [39]	There is no evidence which suggests immune response to COVID-19 will be impaired in asthma patients treated with anti-IL5, anti-IL5Ra, anti-IL4/IL13, or anti-IgE medications. In the absence of any data indicating a potential for harm, it would be reasonable to continue administration of biologic agents during the COVID-19 pandemic in patients for whom such agents are clearly indicated and have been effective.
ACAAI www.college.acaai.org April 8th 2020	For patients with severe asthma currently on a biologic therapy, there is no information at this time that these treatments should be stopped. These severe asthma patients are at an increased risk to COVID-19 infection and optimal control of their chronic condition is of upmost importance.
AAD (Guidance March 20th 2020,www.aad.org)	Patient should not stop biologics without consulting their physician! 1. Non-infected and no symptoms → physicians should continue to weigh the risk vs. benefits of the use of biologic medication on a case-by-case basis based on

	a. the original indication b. the severity of the original indication, c. the patient's age (>60 years) d. comorbidities related to higher risk of mortality in case of COVID-19 2. Patients on biologic therapy positive for COVID-19: recommend to discontinue or postpone the biologic therapy until the patient recovers from COVID-19. Patients being considered for biologic therapy initiation: risk vs. benefits a. Low-risk patients → case-by-case basis. b. High-risk population → recommendation that physicians consider deferring initiation of biologic therapy.
BSACI www.bsaci.org Aptil 5th 2020	• Defer commencement of omalizumab in new patients until COVID-19 restrictions are lifted. • Administer home omalizumab therapy earlier than the fourth dose specified in the product information, by administering training at the second dose and transitioning to home therapy for the third dose. While home therapy is not licensed where there is a history of anaphylaxis of any cause, in cases where there is a clear trigger and no association with omalizumab doses home therapy could be used. In this case consider provision of a written anaphylaxis action plan and adrenaline autoinjectors, if not already done."
DGAKI www.dgaki.de April 8th 2020	• Unavailable therapy with biologics may lead to many patients requiring treatment with systemic steroids and potentially negative impact on immune responses directed against SARS-CoV2 • Stopping treatment with biologics may lead to worsening of the underlying disease, which may therefore provide negative influence on the course of acquired COVID-19 disease. According to WHO patients with chronic lung disease (e.g. such as asthma) may be prone to more severe disease. o viral asthma exacerbations occur less frequently and with

	lower severity under treatment with biologics o those immune-processes targeted by biologics most probably don't affect virus defense • Based on current knowledge we therefore recommend to maintain treatment based on a joint agreement between treating physician and patient.
WAO worldallergy.org April 8th 2020	For patients: "There is currently no evidence that inhaled corticosteroids (nasal or bronchial), antihistamines or biologic medications have any effect on the risk of contracting COVID-19. If you stop or modify your treatment, you run the risk that your allergic disease, particularly your asthma control, could become worse, causing you to need rescue medical treatment or be admitted to the hospital." https://www.worldallergy.org/UserFiles/file/Allergic_patients_during_COVID-19.pdf
PAS[49]	• It is recommended to continue biologic therapy with anti-IgE or anti-IL-5 in patients with severe asthma. • It is acceptable to start and then continue biologic therapy with anti-IgE or anti-IL-5 antibodies in patients with severe bronchial asthma in accordance with the current Biological Treatment Programme of the National Health Fund. • Continuation and, in specific cases, initiation of biologic therapy with anti-IgE antibodies (omalizumab) in patients with severe chronic urticaria is acceptable.

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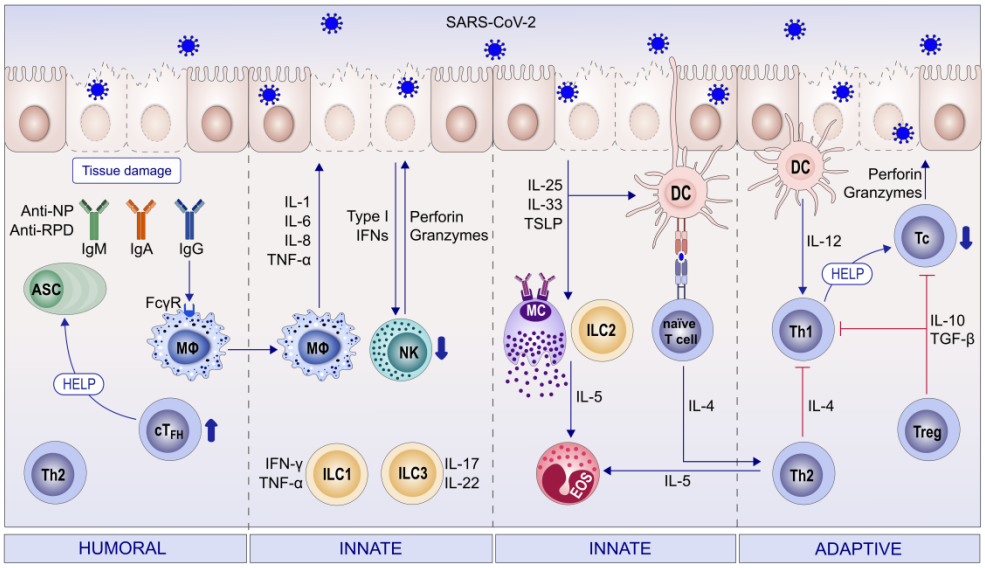

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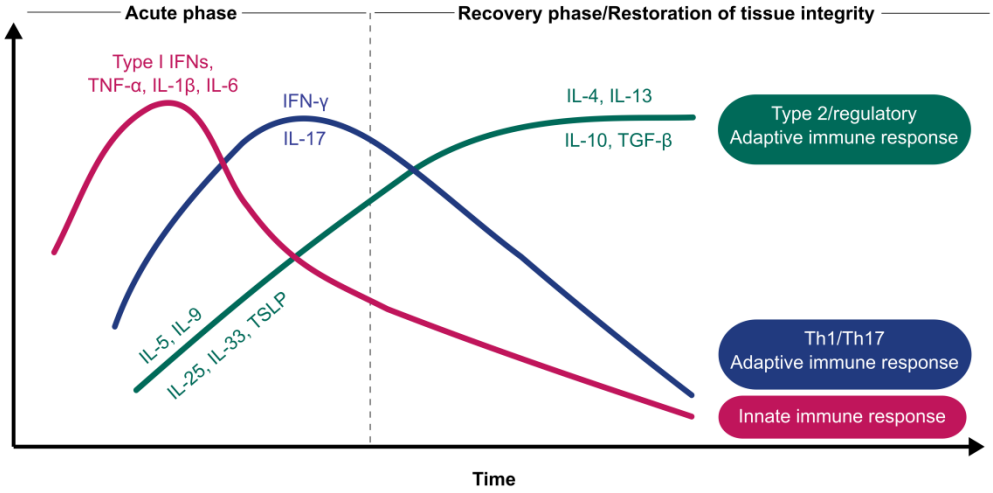

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COVID-19 PANDEMIC

Maintain Add-On Therapy*

Maintain biological treatment

If possible, self application of biological
Assure disease control via regular follow-up via telemedicine

NO INFECTION

Asymptomatic, mild-moderate
SARS-CoV-2 pos
(home isolation)

Severe-critical
(hospital admission)

Witholding of biological treatment for a minimum of 2 weeks until recovered and/or negativity of swab analysis for SARS-CoV-2

Maintain other asthma medication
Intense follow-up (TM)

Acute management of respiratory distress syndrome

COVID-19 (INFECTION)

Re-establish pre-infection treatment
Assess allergic disease severity/control

RECOVERED NON-INFECTIOUS

* In accordance with recommendations on the management of the respective allergic diseases